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14. ABSTRACT Breast cancer cells are known to bear determinants that would allow tumor specific immune responses. However, initiation and amplification of such immune responses are critically dependent upon the balance in TH1 and TH2 cytokine profiles. This molecular epidemiological study evaluates the impact that variability in cytokine profiles, (inferred from functional polymorphisms in cytokine genes), may have on breast cancer risk among urban African-American women. In the first phase of the study, DNA collected and approved for additional study as part of a previously funded Case-Control investigation (n=1600) will be assessed for cytokine polymorphisms. Because cytokine profiles are also known to be affected by environmental factors, particularly levels of stress, this study also evaluates the relative contribution of genotype and stress influences using data collected for that purpose from a sub-sample of healthy Controls (n=400) recruited from the "graduates" of the larger study. Results will allow evaluation of the possibility that deficits in cytokine responses due to genetic or environmental factors may contribute to breast cancer risk. Based on these findings, women at risk for breast cancer because of polymorphisms in genes important to effective immune surveillance could be targeted for innovative prevention strategies including stress reduction and immune modulators.					
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**Immune surveillance, cytokines and breast cancer risk:
Genetic and psychological influences in African American women**

Principal Investigator: Dr. Dana H. Bovbjerg

INTRODUCTION:

Ineffective immune surveillance against newly transformed cells may contribute to increased risk of breast cancer. One mechanism underlying ineffective surveillance, and hence, increased breast cancer risk, may be dysregulation of cytokine production profiles. We hypothesize that women whose cytokine responses tend to favor humoral (Type 2) over cell-mediated (Type 1) responses are at risk for developing breast cancer. A molecular epidemiologic approach is the best method for testing this hypothesis as assessments of cytokine responses in blood samples from patients are likely to be affected by the presence of clinical disease and its treatment. Data suggesting the utility of such an approach to exploring this possible source of breast cancer risk has begun to appear in the literature (e.g., Smith et al. 2004). Little is currently known about such effects in African American women. In the context of a previously funded case-control study (n=1600), we are evaluating the role of polymorphisms in cytokine genes associated with dysregulation in relation to breast cancer risk. In a sub-sample of healthy control subjects (n=400), we are also exploring the relative contribution of genotype (cytokine polymorphisms) and environmental influences (e.g., stress-induced immune modulation) to cytokine responses.

The study is linked to two similar projects (Ambrosone, PI), one approved for funding as part of a Behavioral Center of Excellence award from the Army (DAMD-17-01-1-0334, Bovbjerg, PI) and the other funded by NCI. These “parent” projects draw on collaborations with physicians at the NYC hospitals that have the largest referral patterns for African-Americans in Manhattan, Bronx, Brooklyn and Queens to recruit newly diagnosed African-American breast cancer patients. Age-matched controls are selected using Random Digit Dialing (RDD). Patients consenting to participate undergo an interview and provide a blood specimen for DNA extraction. For our piggy-backed study, appropriate banked DNA can be genotyped for the cytokine polymorphisms of interest. Additional newly obtained blood specimens from consenting Control participants (n=400) are processed for cytokine responses (phenotype), and an additional set of questionnaires focused on psychological stress is completed at the time of the blood draw. Data analyses will be conducted using standard approaches when required sample sizes are reached.

This study synthesizes concepts from behavioral research and molecular epidemiology to address critical questions regarding breast cancer etiology. By exploring hypotheses related to psychoneuroimmunology and using technology and paradigms from molecular epidemiology, this research may make important contributions to identifying causes of breast cancer so that it may be eradicated. By examining case-control differences in cytokine polymorphisms, the role of this aspect of immune function in breast cancer may be elucidated. Furthermore, the evaluation of stress effects on cytokine responses in vitro, particularly in relation to genotype, may provide compelling

support for a possible role of stress in breast cancer etiology.

BODY:

Statement of Work

- Task 0: Successful application for HSRRB approval through USAMRAA office
- Task 1: Setting up study procedures
- Task 2: Inclusion of 1600 Case and Control participants for genotyping
- Task 3: Inclusion of 400 Control participants for phenotyping
- Task 4: Cytokine evaluation of frozen stimulated samples
- Task 5: Analysis of acquired cellular event flow cytometry data
- Task 6: Statistical analysis of cytokine genotype data and preparation of manuscripts
- Task 7: Statistical analysis of cytokine phenotype data and preparation of manuscripts

As previously reported, we have completed Tasks 0 and 1. From July 22, 2005 to July 21, 2006, our first full year of study enrollment (HSRRB approval granted in November 2004), we have made good progress in Tasks 2-5. This has been facilitated by additional funding received from the NCI (Ambrosone, PI) to expand the case-control study, which has greatly sped the pace of recruitment. We now have access to DNA from 811 Case and Control participants, which can be batch genotyped for the cytokine polymorphisms of interest. We have established procedures for coordination with the Molecular, Diagnostic and Research Core of the "parent" Behavioral Center of Excellence (Bovbjerg, PI). We have been contacting Control participants for inclusion in the phenotyping portion of this study. We have identified 181 potential eligible subjects based on database review. Of those, 65 women were found to be ineligible, 32 were lost to follow-up, and 32 refused. We have completed 36 interviews and the remaining 16 are in process.

With a full year of recruitment behind us, we have discovered that we over-estimated the proportion of Control participants from the parent studies who are eligible, and available, for participation in the phenotyping study. This issue will be in part addressed by the addition of more recruiting hospitals in the parent study on which this study is piggy-backed, which has the effect of increasing both cases and controls, as they are recruited at a yoked pace. In addition, we anticipate requesting a no-cost extension to the grant period. We expect to continue to be in line with our estimate in our 2004 annual report of a 24-month delay in tasks 2-7 of our Statement of Work.

KEY RESEARCH ACOMPLISHMENTS:

Task 2: 811 Case and Control participants included for genotyping study

Task 3: 181 Control participants assessed for inclusion into phenotyping study; 36 interviews completed

REPORTABLE OUTCOMES:

At this point in the research, no reportable outcomes are yet available.

CONCLUSIONS:

If the results of the proposed research are consistent with study hypotheses, the study could have profound implications for the eradication of breast cancer. The results of the proposed research may suggest new means of evaluating genetic risk of breast cancer in healthy women, as well as novel intervention strategies for long term reduction of that risk, including stress reduction, as well as biological response modifiers designed to ameliorate dysregulation of cytokine profiles.

REFERENCES:

Smith KC, Bateman AC, Fussell HM, Howell WM. Cytokine gene polymorphisms and breast cancer susceptibility and prognosis. Eur J Immunogenet. 2004 Aug;31(4):167-73.

APPENDICES:

None